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| 10/003,463 | 12/06/2001 | Luis Enrique Fernandez Molina | 3035-102 | 4352 |

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| EXAMINER | |
|---|---|
| GODDARD, LAURA B | |

| ART UNIT | PAPER NUMBER |
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| 1642 | |

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| 02/23/2009 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/003,463 | MOLINA ET AL. | |
| | Examiner | Art Unit | |
| | LAURA B. GODDARD | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3-13 and 21-29* is/are pending in the application.

4a) Of the above claim(s) *12,13 and 21-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 November 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. The Amendment filed November 24, 2008 in response to the Office Action of July 28, 2008, is acknowledged and has been entered. Claims 1, 3-13, 21-29 are pending. No claims were amended. Claims 12, 13, and 21-26 remain withdrawn. Claims 1, 3-11, and 27-29 are currently being examined as drawn to the elected species HER-1, oily adjuvant, and polypeptide antigen.

***Priority/Oath/Declaration***

2. This application claims priority to and Applicants submitted the foreign priority document Cuban Patent Application No. 166/2001, filed on July 12, 2001, however Applicants noted with the foreign document submission dated April 5, 2002, that the Cuban Patent Office has changed the serial number of this Cuban Patent Application from 166/2001 to 167/2001 and Applicants stated: "It is planned to file a substitute declaration to reflect this change." It is noted that no substitute declaration has been submitted to reflect this change. Appropriate correction is required (see section 3 of the previous Office Action).

Applicants state that they are in the process of obtaining the necessary signatures for the substitute declaration. Appropriate correction is still required.

**New Rejections**

(based on new considerations)

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1, 3-11, and 27-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are indefinite because claim 1 recites the phrase "**wherein the antigen is not structurally changed**." This phrase renders the claim indefinite because it the term "not structurally changed" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, while the instant specification discloses administering low immunogenic peptides that are an extracellular domain of HER-1 (EGFR) or HER-1 without a transmembrane region, these peptides would be considered structurally changed compared to the parent HER-1 receptor, however, relative to selected sequences of the parent receptor, they would not be structurally changed. Given the above reasons, the metes and bounds of the claims cannot be determined.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 3-11, and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,788,985, Rodriguez et al., issued 8/4/98 (IDS), in view of Estevez et al (Vaccine, August 2000, 18:190-197), US Patent 4,857,637, Hammonds et al., issued 8/15/89 and Udayachander et al (Human Antibodies, 1997, 8:60-64).

The claims are drawn to a pharmaceutical composition that potentiates immunogenicity of low immunogenic antigens comprising (s) one or more low immunogenic antigens, wherein the low immunogenic antigen is a polypeptide and (b) a vaccine carrier consisting of very small size proteoliposomes (VSSPs), wherein the VSSPs are derived from the Outer Membrane Protein Complex (OMPC) of *Neisseria meningitides* wherein gangliosides have been incorporated into the OMPC, wherein the antigen is not structurally changed and is not incorporated into the VSSPs and wherein the vaccine carrier stimulates and potentiates both humoral and cellular immune responses against the antigen (claim 1), wherein the low immunogenic antigen is a growth factor receptor (claim 3), wherein the extra-cellular domains of the growth factor receptor may or may not contain the trans-membrane region (claim 4), wherein the growth factor receptor is HER-1 (claims 5, 29), wherein the *Neisseria meningitides* is either a wild type or genetically modified strain (claim 6), wherein the VSSPs are obtained by hydrophobically incorporating the gangliosides into the OMPC (claim 7), wherein the gangliosides are GM3 or their N-glycolylated variations (claim 8), wherein the adjuvant is an oily adjuvant and is Incomplete Freund's Adjuvant (claims 9 and 10), the composition of claim 10 wherein the Incomplete Freund's adjuvant is Montanide ISA

51 (claim 11), and the composition of claim 1 wherein the composition further comprises one or more adjuvants (claim 27).

US Patent 5,788,985 teaches a pharmaceutical composition comprising an Outer Membrane Protein Complex (OMPC) of *Neisseria meningitides* wherein gangliosides have been incorporated into the OMPC (Examples 2-4). US Patent 5,788,985 teaches that the pharmaceutical composition increases the immune response against N-glycolylated ganglioside, especially N-glycol GM3 (NGcGM3), which can be used for the treatment of cancer (col. 1, lines 1-12), especially breast cancer which has a higher expression of gangliosides GM3 and GD3 compared to normal breast tissue (abstract; col. 1, lines 59-63 and Example 6), hence gangliosides are targets in treatment approaches (col. 1, lines 64-66). US Patent 5,788,985 teaches the incorporation of gangliosides, including the hydrophobic incorporation of NGcGM3, into the OMPC (col. 2, lines 30-36; col. 3, lines 1-20; Example 2), wherein the *N. meningitides* would be expected to be a wild-type strain (col. 6, lines 1-3).

US Patent 5,788,985 does not teach the pharmaceutical composition further comprising the low immunogenic antigen HER-1 or Incomplete Freund's adjuvant (IFA), wherein the IFA is Montanide ISA 51.

Estevez et al teach that immunization using VSSPs derived from the OMPC of *Neisseria meningitides* with gangliosides incorporated into the OMPC, resulted in significant levels of T-dependent IgG1, IgG2a and IgG2b (cellular) as well as T-independent IgG3 and IgM (humoral) immune responses, wherein no reactogenicity was observed when self-gangliosides were used for immunization. VSSP overcame

natural tolerance to the low-immunogenic self-antigen gangliosides in an adjuvant-dependent fashion (abstract; p. 196, col. 1; Fig. 4). It is known that serotype proteins, which are the main components of the OMPC, induce proliferation and activation of lymphocytes and lead to secretion of IL-2 (p. 196, 1st column, last paragraph to 2nd column). Estevez et al teach immunization using Incomplete Freund's Adjuvant Montanide ISA 51 with the VSSPs derived from the OMPC of *Neisseria meningitides* and gangliosides incorporated into the OMPC (p. 191, col. 2; Table 1; Fig. 4 and 7). Estevez et al teach that Montanide ISA 51 is preferred because it is less toxic than Incomplete Freund's Adjuvant (p. 191, col. 2). Immunization of mice with VSSPs derived from the OMPC of *Neisseria meningitides* and gangliosides incorporated into the OMPC in combination with Montanide ISA 51 resulted in increased immunoglobulin titers compared to mice immunized with the VSSP composition without Montanide ISA 51 (p. 194, col. 2; Table 1). Estevez et al teach that patients suffering from metastatic breast cancer have been immunized with GM3/VSSP and NGcGM3/VSSP vaccines in Montanide ISA 51 for therapy (p. 196, col. 2).

US Patent 4,857,637 teaches a pharmaceutical composition comprising the polypeptide epidermal growth factor receptor (EGFR, also known as HER-1) as an antigen to immunize animals against the EGFR (col. 3, lines 36-43; col. 4, lines 58-63). US Patent 4,857,637 teaches that EGFR is overexpressed in malignant cells and is a desirable target for therapy (col. 3, lines 63-66; col. 4, lines 26-38). Immunization may comprise administering growth factor receptor derivatives or intact receptors, which would not be structurally changed (col. 4, lines 57-61). Growth factor receptors

comprise extracellular, transmembrane and cytoplasmic domains, wherein immunization of a receptor comprising the extracellular domain is desirable because the extracellular domain is accessible to antibodies under *in vivo* conditions, unlike the intracellular or cytoplasmic domains (col. 8, lines 47-68). US Patent 4,857,637 teaches the immunization of growth factor receptors with an adjuvant, such as Incomplete Freund's, because poorly immunogenic proteins are rendered more immunogenic by the use of adjuvants (col. 4, lines 63-68; col. 5, lines 50-55; col. 7, lines 1-3; col. 18, lines 50-55).

Udayachander et al teach that many malignancies, such as breast cancer, overexpress EGFR and EGFR is a target for therapy (abstract).

These references suggest the importance of each of the claimed pharmaceutical composition components in stimulating an immune response to the ganglioside or EGFR antigen. However, the references are deficient in that they do not teach using these components together. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the Outer Membrane Protein Complex (OMPC) of *Neisseria meningitides* wherein ganglioside antigens have been incorporated into the OMPC taught by US Patent 5,788,985 and Estevez et al, and the EGFR (HER-1) antigen taught by US Patent 4,857,637 in combination in order to treat malignant tumors that overexpress these two antigens, such as breast cancer, because US Patent 5,788,985 teaches that breast cancer overexpresses ganglioside GM3 and Udayachander et al teach that breast cancer overexpresses HER-1. One of ordinary skill in the art would have been motivated to use the two pharmaceutical components in

combination in a method of treating a malignant tumor that overexpresses the two antigens, such as breast cancer, in view of the importance of targeting these two antigens for cancer therapy. Each of these agents had been taught by the prior art to be therapeutic targets in the treatment of malignant tumors, such as breast cancer, thus the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two modes of treatment, each of which is taught by the prior art to be useful for the same purpose in order to make a protocol that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. One of ordinary skill in the art would have reasonably expected to obtain effective therapeutic targeting of malignant tumors, such as breast cancer, with either or both of these agents since both are taught in the prior art to be used to illicit an immune response specific to the target cancer antigen.

Similarly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use Incomplete Freund's adjuvant (IFA) or the IFA Montanide ISA 51 in addition to the two pharmaceutical components because adjuvant is conventionally used in pharmaceutical compositions, US Patent 4,857,637 teaches that poorly immunogenic proteins are rendered more immunogenic by the use of adjuvants such as IFA, and Estevez et al demonstrate Montanide ISA 51 increases antibody production. One would have been motivated to add IFA or Montanide ISA 51 to the pharmaceutical composition taught by the combined references in order to boost the immune response to the antigens for therapeutic purposes.

Although the references do not teach that the composition stimulates and potentiates both humoral and cellular responses against the HER-1 (EGFR) antigen the pharmaceutical composition taught by the combined references comprises the same components as the instantly claimed composition hence, the pharmaceutical composition taught by the prior art would necessarily induce both a humoral and cellular immune response against a low immunogenic antigen such as HER-1.

**Response to Relevant Arguments**

5. Some of Applicants' arguments in the response mailed 4/23/2008 are relevant to the rejection above. Applicants argue that the prior art does not teach the adjuvant property of VSSPs for low immunogenic peptides as Applicants surprisingly found. Applicants argue that in the prior art, low immunogenic peptides are structurally modified to contain a hydrophobic tail to be incorporated into the OMPC of *Neisseria meningitides* (proteosomes) when administered to induce humoral and cellular immune responses, hence the prior art does not teach administering peptides that are not structurally changed. Applicants argue that such chemical modification usually renders neo-antigens with important changes in immune dominance, basically for the TCD8+ effector cell repertoire, and limits the antigenic universe that can be used. Applicants argue that claim amendments to indicate the antigen is not structurally changed distinguishes the present invention for teachings of the prior art (p. 11). Applicants argue that the prior art does not suggest combining a low immunogenic peptide antigen with a VSSP without incorporating the peptide into the lipid bilayer of the VSSP without

structurally modifying the peptide or that the VSSPs act as adjuvant for an unincorporated peptide, hence the present invention is unexpected and the art teaches away from the invention (p. 12). Applicants argue that a surprising property of the VSSPs is the immune potentiating effect, particularly activating CD8+ T effector cells (p. 12). Applicants reiterate that the present invention is based on the surprising finding that VSSPs are able to function as an adjuvant for low immunogenic peptide antigens that are not incorporated into the VSSPs and not structurally changed, and this adjuvant property is not taught or suggested in the prior art (p. 13).

6. The arguments have been considered but are not found persuasive. Although the references do not teach using the pharmaceutical composition agents together, Examiner maintains it is obvious to combine two modes of treatment, each of which is taught by the prior art to be useful for the same purpose in order to make a protocol that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. One of ordinary skill in the art would have reasonably expected to obtain effective therapeutic targeting of malignant tumors, such as breast cancer, with either or both of these agents since both had been demonstrated in the prior art to successfully illicit an immune response specific to the target cancer antigen. Given the pharmaceutical composition taught by the combined references comprises the same components as the instantly claimed composition hence, the pharmaceutical composition taught by the prior art would necessarily induce

both a humoral and cellular immune response against a low immunogenic antigen such as HER-1.

Examiner maintains that the adjuvant properties of VSSPs for the induction of cellular and humoral immune responses to low immunogenic peptides were known in the prior art and not surprising. Although the prior art (below) teaches using the VSSPs as carriers by incorporating the peptide antigens into the proteosomes, the prior art teaches that these proteosomes also act as adjuvants for the low immunogenic peptides. US Patent 5,726,292, Lowell, issued March 10, 1998 teach improved immunopotentiating systems for low immunogenic antigens that are proteins, polypeptides, peptides comprising incorporating the antigens into proteosomes derived from the OMPC of *Neisseria meningitidis* (abstract). US Patent '292 teaches that the non-immunogenic peptide antigen can be made immunogenic by complexing them to the proteosomes wherein they can be used as a vaccine against malignancies (col. 6, lines 21-26 and 24-40) and induce a cell-mediated T-cell response or humoral antibody response (col. 4, lines 19-26). Lowell et al (Science, 1988, 240:800-802) teach that proteosomes complexed with low immunogenic malaria CS peptides enhanced immune response to the peptides (abstract; p. 802, col. 2). Lowell et al teach that the proteosomes act as adjuvants since they are B cell mitogens (p. 800, col. 2; p. 802, col. 1) and teach that immunity is most enhanced when a peptide is linked to both carrier protein and adjuvant in the same molecule (p. 802, col. 1). Levi et al (Vaccine, 1995, 13:1353-1359) teach that influenza peptides coupled to proteosomes induced effective specific humoral and cellular immune responses as well as a significant protective effect

against viral challenge (p. 1354, col. 1). Levi et al teach that proteosomes act as both carrier and adjuvant for the peptide-based vaccine (p. 1357, col. 1). VanCott et al (J of Immunology, 1998, 160:2000-2012) teach that HIV peptides coupled to proteosomes resulted in induced neutralizing antibody responses to the virus and that proteosomes have known adjuvant properties (p. 2008, col. 2 to p. 2009, col. 1). Given the extensive teachings in the art for the known adjuvant properties of proteosomes derived from the OMPC of *Neisseria meningitides* for divergent peptides, the adjuvant effect of combining HER-1 peptide with VSSPs is not surprising. The prior art recognizes repeatedly that the proteosomes act as *both* carrier and adjuvant and that the proteosomes themselves have adjuvant properties. Whether the peptide is coupled to the proteosome or not, it is clear from the prior art that the proteosome confers enhanced immune responses to the peptide it is administered with because of its adjuvant properties.

Although Applicants argue that the peptides of the prior art are structurally altered in order to be coupled to the proteosome, the instant specification and claims do not define what an antigen "not structurally changed" is relative to any other antigen. The peptide antigens of the prior art had hydrophobic anchors attached to complex them to the proteosomes, however the peptide antigens themselves were not structurally changed or mutated compared to the wild-type antigen, and the prior art (above) teaches that the immune responses to the peptides were specific and neutralizing. The HER-1 antigen taught by US Patent 4,857,637 used in the method of the combined references in the rejection above is not structurally changed relative to

HER-1 for similar reasoning. The pharmaceutical composition taught by the combined references, beneficial for treating breast cancer, comprises the same agents in the instantly claimed composition, hence the pharmaceutical composition taught by the combined references would necessarily induce both a humoral and cellular immune response against a low immunogenic antigen such as HER-1. The adjuvant properties of proteosomes for inducing humoral and cellular responses to low immunogenic peptides in the prior art are known and reasonably expected for the composition taught by the combined references.

7. All other rejections recited in the Office Action mailed July 28, 2008 are hereby withdrawn.

8. **Conclusion:** No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard/
Primary Examiner, Art Unit 1642